REMARKS

In a final Office Action mailed on January 27, 2009, claims 1-4, 6, 8-21, 23-24, and 43-48 were rejected. Claims 1-4, 6, 8-21, 23-24, 32-39 and 43-48 are pending. Claims 32-39 have been withdrawn as being drawn to non-elected inventions. Claims 5, 7, 22, 25-31, and 40-42 are canceled. Applicants respectfully request reconsideration of these pending claims.

I. Rejection under 35 USC § 103

Claims 1-4, 6, 8-21, 23-24, and 43-48 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Claasen *et al.* (Vaccine, 1996, 14/10:1001-1008), Garcon *et al.* (WO 98/56414), in view of Krieg *et al.* (WO 98/18810) and Schwartz *et al.* (WO 98/55495). Applicants traverse the rejection and its supporting remarks.

A. Insufficient Rationale to Combine the References

Applicants respectfully assert that the Examiner has not yet provided a sufficient rationale to explain why one of skill in the art would have selected four random references to combine them to produce the claimed invention. On page 8 of the latest Office Action, dated 1/27/09, the Examiner addresses the applicants arguments and "recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge of one of skill in the art." But then the Examiner merely goes on to reiterate the contents of the original Office Action and recites *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). However, the Supreme Court in *KSR* stated:

> As is clear from cases such as Adams, *a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.* Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a* ***reason*** that would have prompted a person of ordinary skill in the

> relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. Id at 1741.

Examiner appears to have provided two rationales, one from *KSR* and one from MPEP 2141.III , discussing *KSR*. First, the Examiner provides the following quote from *KSR*, "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield ***predictable results***." Second, the Examiner states, "it would be obvious to apply a known technique to a known product to be used in a known method that is ***ready for improvement*** to ***yield predictable results***." See page 12, lines 15-23, of the Office Action dated 1/27/09. Both of these rationales require that the art be predictable. As is discussed in part B below, the art of vaccines and adjuvants is far from predictable. Given the lack of predictability, neither rationale is available and therefore, the applicants respectfully assert that a *prima facie* case of obviousness has not been established. If applicants have mis-understood the rationale that the Examiner is relying upon in combining the four references, applicants respectfully request that the Examiner provide additional explanation of the rationale upon which the Examiner is relying so that the applicants may properly respond to the rejection.

B. No Reasonable Expectation of Success – Unpredictable Art

The applicants in their response, dated 11/2/07, asserted that there was no reasonable expectation of success based upon the combined references. In response, the Examiner asserted on page 8, lines 8-10, of the Office Action that "it is noted that Applicants have not specifically claimed that the composition has synergistic immunogenicity." However, the applicants' arguments regarding a synergistic response were not related to the lack of a reasonable expectation of success due to the unpredictable nature of the art. The synergy resulting from the combination is a secondary consideration, i.e., an unexpected result. Although obviousness does not require absolute predictability, at least some degree of predictability that the combination will work is required (MPEP 2143.02.II). The art of selecting adjuvants in order to enhance immune responses to specific antigens is unpredictable as noted in the three adjuvant review articles included herewith.

In the first review article, Aucouturier, *et al.* state: "But there is no universal adjuvants and their action is not yet clear and rely on different mechanisms. Then, they must be adapted according to several criteria, like the target species, the antigens, the type of immune response, the route of inoculation, or the duration of immunity." (*See Vaccine* (2001) 19:2666-2672 at abstract; included with the IDS submitted herewith). Similarly, the second review article by Edelman states: "Every adjuvant has a complex and often multi-factorial immunological mechanism, usually poorly understood in vivo. Many determinants of adjuvanticity exist, and each adjuvanted vaccine is unique. Adjuvant safety is critical and can enhance, retard, or stop development of an adjuvanted vaccine. *The choice of an adjuvant often depends upon expensive experimental trial and error, upon cost, and upon commercial availability.*" (emphasis added; *Molecular Biotechnology* (2002) 21:129-148 at abstract; included with the IDS submitted herewith).

The unpredictability described in Aucouturier, *et al.* and Edelman is further evidenced in a study published by Wuorimaa *et al.* (*J. Infectious Diseases* (2001) 184:1211-1215) included with the IDS submitted herewith. In Wuorimaa *et al.*, a vaccine containing a mixture of pneumococcal capsular polysaccharides of different serotypes conjugated to diphtheria toxoid or tetanus protein carriers was administered with or without aluminum hydroxide (alum) adjuvant. The authors of the study note that "aluminum adjuvant did not seem to provide a significant benefit in immunogenicity, although an overall tendency for higher antibody concentration and relative avidity appeared with the adjuvanted formulation in most serotypes. The data also suggest that differences in the sensitivity to the adjuvant might exist between polysaccharide-protein conjugates; of the 6 types studied, type 5 conjugate benefited from the adjuvant." (p. 1213, second column, line 3 to page 1214, first column, line 4). Thus, the study in Wuorimaa *et al.* illustrates that even within a class of polysaccharide-protein conjugates, one of skill cannot predict which conjugate combination, if any, will benefit from a particular adjuvant without resorting to simple trial and error experimentation.

Finally, the unpredictability of making antigen-adjuvant combinations in order to enhance immune responses to specific antigens is acknowledged in the Krieg *et al.* reference cited by the Examiner: "Further, conventional adjuvants only work for certain antigens, only induce an antibody

(humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). *For many pathogens, the humoral response contributes little to protection, and can even be detrimental.*" (emphasis added; p. 65, lines 5-8). This clearly implies that the Th2 response contributes protection for some pathogens. Krieg *et al.* do not provide any guidance cited by the Examiner to determine which pathogens benefit from a Th2 response and which do no, so one of skill in the art would have to use trial and error to determine this. Furthermore, the Examiner has not cited to any data provided in Claasen *et al.*, Garcon *et al.*, Schwartz *et al.*, and Krieg *et al.* that provide one of skill in the art with a predictable solution for generating a composition with synergistic immunogenicity and therefore a reasonable expectation of success in combining a *Neisseria* antigen with an oligonucleotide comprising at least one CG motif and an emulsion comprising submicron oil droplets and an emulsifying agent. Because there is no reasonable expectation of success, one of skill would not have made the claimed vaccine formulation. Therefore, the adjuvant/antigen combination as claimed in nonobvious and synergistic immunogenicity does not need to be claimed. Withdrawal of the rejection is thus respectfully requested.

C. Unexpected results

In Sections A and B, above, Applicants have demonstrated that the Examiner has not established a *prima facie* case for obviousness. However, even if the Examiner had established a *prima facie* case, unexpected results are provided in the application which can rebut a *prima facie* case (MPEP 2141.V). The unexpected results provided in the application include synergistic immunogenicity, immunogenic response greater than the sum of the response to the antigen with each adjuvant individually, and increased immunogenicity approximately five fold after the first dose and seven fold after the second dose. The Examiner argues that these features are not recited in the rejected claims. Applicants respectfully assert that secondary considerations do not need to be claimed, but are provided as evidence to rebut the alleged *prima facie* case presented by the Examiner. Based upon the data in the specification, the synergistic effect a product of the combination. Applicants respectfully request that the Examiner provide a citation from the MPEP that supports the argument that secondary considerations need to be claimed so that the Applicants

can better understand the Examiner's position. If the Examiner cannot find such support for this assertion, Applicants respectfully request that the Examiner consider the unexpected result even absent inclusion in the claims as applicants understanding is that an unexpected result does not need to be expressly claimed.

In summary, Applicants respectfully assert that a *prima facie* case for obviousness has not been established because no sufficient rationale to combine the references has been provided and there was no reasonable expectation of success to make the claimed vaccine formulation given art recognized unpredictability in adjuvants and adjuvant combinations. Applicants maintain that even if a *prima facie* case for obviousness had been successfully made by the Examiner, it is rebutted by evidence of unexpected results. Withdrawal of the rejection is thus respectfully requested.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002102200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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